VERIFICATION OF TRANSLATION

I, Melissa Stanford, a translator with Chillson Translating Service, 3530 Chas Drive, Hampstead, Maryland, 21074, hereby declare as follows:

That I am familiar with the German and English languages;

That I am capable of translating from German to English;

That the translation attached hereto is a true and accurate translation of German Application 197 18 341.7 titled, "Stents with a Radioactive Surface Coating, Processes for their Production and their Use for Restenosis Prophylaxis" filed with the German Patent Office on April 30, 1997;

That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

And further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any registration resulting therefrom.

By Melissa Stanford

Executed this 11 day of Oct 1999.

Witness Anne Chillson

FEDERAL REPUBLIC OF GERMANY

Certificate

The SCHERING AKTIENGESELLSCHAFT, Berlin/Germany filed a patent application under the designation

"Stents with a Radioactive Surface Coating, Processes for their Production and their Use for Restenosis Prophylaxis"

with the German Patent Office on April 30, 1997.

The attached copies are a true and accurate rendition of the original document of this patent application.

In the German Patent Office the application has provisionally received the symbols A 61 M, A 61 F and A 61 L of the International Patent Classification.

[Seal]

Munich, July 15, 1998

For the Director of the German Patent Office

/s/

Agurks

File No.: 197 18 341.7

Stents with a Radioactive Surface Coating, Processes for their Production and their Use for Restenosis Prophylaxis

The invention relates to stents with a radioactive surface coating, processes for their production by chemical deposition of solutions and their use for restenosis prophylaxis.

Prior Art

Radioactive stents are prior art (EP 0433011, WO 94/26205, US 5176617). Stents are self-expanding endoprostheses that make it possible to keep open duct-like structures in the bodies of humans or animals (e.g., vascular, esophageal, tracheal and bile duct stents). They are used as palliative measures in the case of stenoses by obstruction (e.g., arteriosclerosis) or external pressure (e.g., in the case of tumors). Radioactive stents are used, for example, after vascular-surgery interventions or radiological interventions (e.g., balloon angioplasty) for restenosis prophylaxis. Such radioactive stents can be produced, for example, by activation of a non-radioactive stent using irradiation with protons or deuterons from a cyclotron (WO 94/26205).

There is now the problem that, on the on hand, generally no cyclotron is available at the site of the use of the stent to undertake an activation of the stent, and, on the other hand, the activated stent cannot be transported in any arbitrary way due to the sometimes short half-life of the activated isotope and for reasons of protection against radiation.

The object of this invention is therefore to make available stents that can be activated independently by a cyclotron. In particular, the object of the invention is to make available stents that can be coated independently by a cyclotron with a preselected radioactive isotope.

This object is achieved by the stents that are described below as they are characterized in the claims.

Description of the Invention

The above-described object is achieved according to the invention by a chemical deposition of the radioactive isotope on the stent.

To this end, the selected stent is immersed in a solution that contains the radioactive isotope. The radioactive isotope is then chemically deposited on the stent. Depending on the selected material of the stent, on the one hand, and the radioactive isotope that is to be deposited, on the other hand, two possible types of deposition are considered:

1) Chemical R duction

During chemical reduction, a reducing agent (e.g., $SnCl_2$, KBH_4, dimethylborane, formaldehyde, sodium hypophosphite) is added to the solution that contains the radioactive isotope in dissolved form as well as the stent.

After 1 minute to 10 hours, the stent is removed from the respective solution and washed. The stent is coated on the surface with the radioactive isotope.

In this way, for example, radioisotopes of elements Ag, Au, Ba, Bi, Co, Cr, Cu, Fe, Ga, Gd, Hg, Ho, In, Ir, Lu, Mn, Pb, Pd, Pm, Re, Rh, Ru, Sb, Sc, Sm, Tb, Tc or Y can be deposited on metal stents (e.g., steel, nitinol).

2) Chemical Precipitation

During chemical reduction, a precipitating agent (e.g., oxalic acid, phosphoric acid or salts thereof or Na_2CO_3) is added to the solution that contains the radioactive isotope in dissolved form as well as the stent.

In this way, for example, radioisotopes of elements Ag, Au, Ba, Bi, Co, Cr, Cu, Fe, Ga, Gd, Hg, Ho, In, Ir, Lu, Mn, Pb, Pd, Pm, Re, Rh, Ru, Sb, Sc, Sm, Tb, Tc or Y can be deposited on metal stents (e.g., steel, nitinol).

The invention therefore relates to radioactive stents, characterized in that the stent is coated on the surface with the radioactive isotope, as well as processes for their production.

The above-described processes are generally performed at temperatures of 0-100°C. In the coating of the stent, non-

aqueous solvents can also be used on the basis of the isotope that is to be deposited. When a non-aqueous solvent is used, the latter is to be removed before the implantation.

The stents can also be coated with two or more different isotopes. It is possible in particular to apply short-lived and long-lived isotopes together on a stent (for example, ^{55}Co with ^{55}Fe, or ^{99}Mo with ^{57}Co).

The operations that are necessary for implementing the above process that is described in principle are known to one skilled in the art. Special embodiments are described in detail in the examples.

The stents according to the invention achieve the above-described object. Stents can be radiolabled easily by the disclosed processes and metered precisely. The stents according to the invention are readily physiologically compatible. As it was possible to show in the animal model, the restenosis is significantly inhibited after balloon denudation by implantation of the stents according to the invention.

The special advantage of the stent according to the invention is that the physician can select on the spot a (non-radioactive) stent according to his needs and can then activate the selected stent by the described process. The few substances and solutions that are required for this purpose can be supplied prepared accordingly, so that the corresponding physician need only immerse the uncoated stent in the individual solutions in the specific sequence. The invention thus also relates to those

substances, solutions and preparations (kits) that are prepared for the processes according to the invention.

Embodiments:

The following examples are to explain the subject of the invention, without intending that it be limited to these examples.

Example 1

Y-90-Direct Labeling of a Wiktor Stent

A Wiktor stent (22.85 mg, model 6570, Medtronic) is covered with a layer of 2 ml of saturated sodium oxalate solution. 37 MBq of yttrium-90-trichloride solution is added and heated for 30 minutes to 60°C. Then, the stent is removed and washed three times with 5 ml of 0.9% sodium chloride solution. The thus labeled Wiktor stent carries an activity of 0.88 MBq of Y-90.

Example 2

Tc-99m-Coating of Strecker Stents

A strecker stent (6.51 mg, SS/5-4, Boston Scientific) is covered with a layer of 726 µl of sodium pertechnetate solution (231.9 MBq). 100 µl of tin(II)-chloride dihydrate solution (5 mg of $SnCl \cdot 2H_2O$/1 ml of 0.01 M HCl) is added, the reaction mixture is put into an ultrasound bath for 5 minutes and finally incubated for 25 minutes at room temperature. The stent is dried and washed three times for 15 minutes with 726 µl of 0.9% sodium chloride solution. Finally, it is again covered with a layer of 726 µl of 0.9% sodium chloride solution, and the reaction mixture is put into an ultrasound bath for 5 minutes. The dried Strecker

stent caries an activity of 1.1 MBq-Tc-99m/6.51 mg (≙ 29.7 μCi/6.51 mg ≙ 4.6 μCi/1 mg).

Example 3

Re-186 Coating of Strecker Stents

A Strecker stent (6.60 mg, SS/5-4, Boston Scientific) is covered with a layer of 736 μl of sodium perrhenate solution (240.2 MBq). 100 μl of tin(II)-chloride-dihydrate solution (5 mg of SnCl2 · $2H_2O$/1 ml of 0.01 M HCl) is added, the reaction mixture is put into an ultrasound bath for 5 minutes and finally incubated for 25 minutes at room temperature. The stent is dried and washed three times for 15 minutes with 736 μl of 0.9% sodium chloride solution. Finally, it is again covered with a layer of 736 μl of 0.9% sodium chloride solution, and the reaction mixture is put into an ultrasound bath for 5 minutes. The dried Strecker stent carries an activity of 1.0 MBq-Re-186/6.6 mg (≙ 27 μCi/6.6 mg ≙ 4.1 μCi/1 mg).

Example 4

Tc-99m Coating of Strecker Stents

A Wiktor stent (22.92 mg, model 6570, Medtronic) is covered with a layer of 2.56 ml of sodium pertechnetate solution (911.5 MBq). 256 μl of tin(II)-chloride-dihydrate solution (5 mg of $SnCl_2 \cdot 2H_2O$/1 ml of 0.01 M HCl) is added, the reaction mixture is put into an ultrasound bath for 5 minutes and then incubated for 25 minutes at room temperature. The stent is dried and washed three times for 15 minutes with 2.56 ml of 0.9% sodium chloride

solution. Finally, it is again covered with a layer of 2.56 ml of 0.9% sodium chloride solution, and the reaction mixture is put into an ultrasound bath for 5 minutes. The dried Wiktor stent carries an activity of 5.9 MBq-Tc-99m/22.92 mg (≙ 159.5 μCi/22.92 mg ≙ 6.9 μCi/1 mg).

Example 5

Re-186 Coating of Wiktor Stents

A Wiktor stent (22.31 mg, model 6570, Medtronic) is covered with a layer of 2.5 ml of sodium perrhenate solution (884.1 MBq). 249 μl of tin(II) chloride dihydrate solution (5 mg of $SnCl2 \cdot 2H_2O$/1 ml of 0.01 M HCl) is added, the reaction mixture is put into an ultrasound bath for 5 minutes and finally incubated for 25 minutes at room temperature. The stent is dried and washed three times for 15 minutes with 2.5 ml of 0.9% sodium chloride solution. Finally, it is again covered with a layer of 2.5 ml of 0.9% sodium chloride solution, and the reaction mixture is put into an ultrasound bath for 5 minutes. The dried Wiktor stent carries an activity of 5.2 MBq-Re-186/22.31 mg (≙ 140.5 μCi/22.31 mg ≙ 6.3 μCi/1 mg).

Example 6

Administration of a Wiktor Stent that is Coated with Tc-99m in the Abdominal Aorta of Rabbits

The Wiktor stent (model 6570, Medtronic) was coated with Tc-99m as described in Example 4. In an anesthetized (Rompun/Ketavet 1:2) white New Zealand rabbit (3.2 kg of body

weight), the femoral artery was exposed. The labeled Wiktor stent was inserted into the vessel via a 5 F sluice and secured in the infrarenal aorta by inflating the balloon catheter. The catheter was then removed, and both the femoral artery and the wound were sutured. Over a period of 8 hours after administration of the stent, whole-body scintigrams were prepared with the aid of a commercially available gamma camera. Five hours after administration of the stent, a scintigram was prepared. Activity could only be located in the area of the stent that is in the infrarenal aorta of the animal. During the entire examination period, no detectable activity was rinsed from the stent. After 8 hours, the rabbit was killed, the stent was removed, and the activity was measured in the gamma counter. The activity that adheres to the stent was equally as high as at the beginning of the test.

Example 7

Labeling of a Strecker Stent with Cu-67

A Strecker stent (1993 mg) in an alkaline copper sulfate/potassium-sodium tartrate solution with an activity of 47.3 MBq is added to a cementation cell (Fig. 2a). After formaldehyde solution is added, the deposition of elementary copper is carried out. The active solution is removed, and the stent is washed four times with physiological common salt

solution. It shows an activity of 1.63 MBq.

Cu $SO_4 \cdot 5H_2O$	500 mg/100 ml
$KNaC_4H_4O_6 \cdot 4H_2O$	2500 mg/100 ml
NaOH	700 mg/100 ml
HCOH (37%)	1 ml/100 ml
T	20°C

Example 8

Labeling of a Nitinol Stent with Au-199

A nitinol stent (496 mg) in a solution that consists of potassium-gold cyanide (K Au-199-$(CN)_4$) with an activity of 137.8 MBq, potassium cyanide, potassium hydroxide and potassium borohydride is added to a cementation cell (Fig. 2b). The temperature is 75°C, and it is stirred for 3 minutes. After 4 minutes, the solution is drained off, and the stent is washed four times with physiological common salt solution. Its activity is 1.31 MBq.

K [Au $(CN)_2$]	580 mg/100 ml
K CN	1300 mg/100 ml
K OH	1120 mg/100 ml
K BH_4	2160 mg/100 ml

Example 9

Labeling of a Strecker Stent with Ag-110

A Strecker stent (997 mg) in a solution that consists of sodium-silver cyanide (Na Ag $(CN)_2$) with an activity of 40 MBq/mg of stent, sodium cyanide, sodium hydroxide and dimethylborane is

added to a cementation cell. It is stirred for 4 minutes at 55°C, then the solution is drained off, the stent is washed four times with physiological common salt solution, and the activity is determined. It is 1.34 MBq.

Na [Ag $(CN)_2$]	183 mg/100 ml
Na CN	100 mg/100 ml
Na OH	75 mg/100 ml
K BH_4	200 mg/100 ml

Na [$Ag(CN)_2$]: 134 mg of AgCN + 49 mg of NaCN

Example 10

Labeling of a Strecker Stent with Pd/P-32

A Strecker stent (1996 mg) in a solution that consists of palladium chloride, hydrochloric acid, ammonia and ammonium chloride is added to a cementation cell (Fig. 2a). The solution has a temperature of 55°C and is stirred. 9 mg of sodium hypophosphite-monohydrate, which has an activity of 36.4 MBq, is stirred into the solution. A palladium-phosphorus alloy, which has an activity of 1.31 MBq, is deposited on the stent.

Pd Cl_2	200 mg/100 ml
HCl (38%)	0.4 ml/100 ml
NH_4OH (28%)	16 ml/100 ml
NH_4Cl	2.7 g/100 ml
$NaH_2PO_2 \cdot H_2O$	1 g/100 ml
T	55°C

3 g of hypophosphate yields 1 g of Pd alloy with 1.5% P

Example 11

Labeling of a High-grade Steel Stent with Pd/P-32

A high-grade steel stent (498 mg) in a solution that consists of palladium chloride, hydrochloric acid, ammonia and ammonium chloride is added to a cementation cell (Fig. 2b). The solution has a temperature of 55°C and is stirred. 6 mg of sodium hypophosphite-monohydrate, which has an activity of 37.8 MBq, is stirred into the solution. A palladium-phosphorus alloy, which has an activity of 1.16 MBq, is deposited on the stent.

$PdCl_2$	200 mg/100 ml
HCl (38%)	0.4 ml/100 ml
NH_4OH (28%)	16 ml/100 ml
NH_4Cl	2.7 g/100 ml
$NaH_2PO_2 \cdot H_2O$	1 g/100 ml
T	55°C

3 g of hypophosphite yields 1 g of Pd alloy with 1.5% P

Example 12

Labeling of a Nitinol Stent with Pd/P-32

A nitinol stent (96 mg) in a solution that consists of palladium chloride, hydrochloric acid, ammonia and ammonium chloride is brought into a cementation cell (Fig. 2b). The solution has a temperature of 55°C and is stirred. 3 mg of sodium hypophosphite-monohydrate, which has an activity of 39.4 MBq, is stirred into the solution. A palladium-phosphorus alloy,

which has an activity of 1.37 MBq, is deposited on the stent.

$PdCl_2$	200 mg/100 ml
HCl (38%)	0.4 ml/100 ml
NH_4OH (28%)	16 ml/100 ml
NH_4Cl	2.7 g/100 ml
$NaH_2PO_2 \cdot H_2O$	1 g/100 ml
T	55°C

3 g of hypophosphite yields 1 g of Pd-alloy with 1.5% P

Example 13

Labeling of a High-grade Steel Stent with P-32

A high-grade steel stent (1992 mg) in a solution of phosphoric acid that is heated to 50°C with an activity of 41.4 MBq is brought into a galvanization cell (Fig. 1). The stent is operated as an anode, and electrolysis is done for 2 minutes at 2 V. Then, the solution is drained off, the stent is rinsed four times with physiological common salt solution, and the activity of the stent is measured. It is 0.93 MBq.

Claims

1. Radioactive stents, characterized in that the stent is coated on the surface with the radioactive isotope.

2. Process for the production of radioactive stents, characterized in that a non-radioactive stent is immersed in a solution that contains at least one radioactive isotope in ionic form, and the isotope is then chemically deposited on the stent.

3. Process for the production of radioactive stents according to claim 2, wherein the isotope is deposited reductively on the stent.

4. Process for the production of radioactive stents according to claims 2 and 3, wherein as a reducing agent, $SnCl_2$, KBH_4, dimethylborane, formaldehyde or sodium hypophosphite is used.

5. Process for the production of radioactive stents according to claim 2, wherein the isotope is deposited on the stent by chemical precipitation.

6. Process for the production of radioactive stents according to claims 2 and 5, wherein as a precipitating agent, oxalic acid, oxalate, phosphoric acid, phosphate or Na_2CO_3 is used.

7. Process according to at least one of claims 2-6, wherein the radioactive isotope is an isotope of elements Ag, Au, Ba, Bi, C, Co, Cr, Cu, Fe, Ga, Gd, Hg, Ho, In, Ir, Lu, Mn, P, Pb, Pd, Pm, Re, Rh, Ru, Sb, Sc, Sm, Tb, Tc or Y.

8. Radioactive stents, wherein the stents are produced by the process according to at least one of claims 2-7.

9. Radioactive stents according to claim 8, wherein several isotopes are deposited on the stent on the surface.

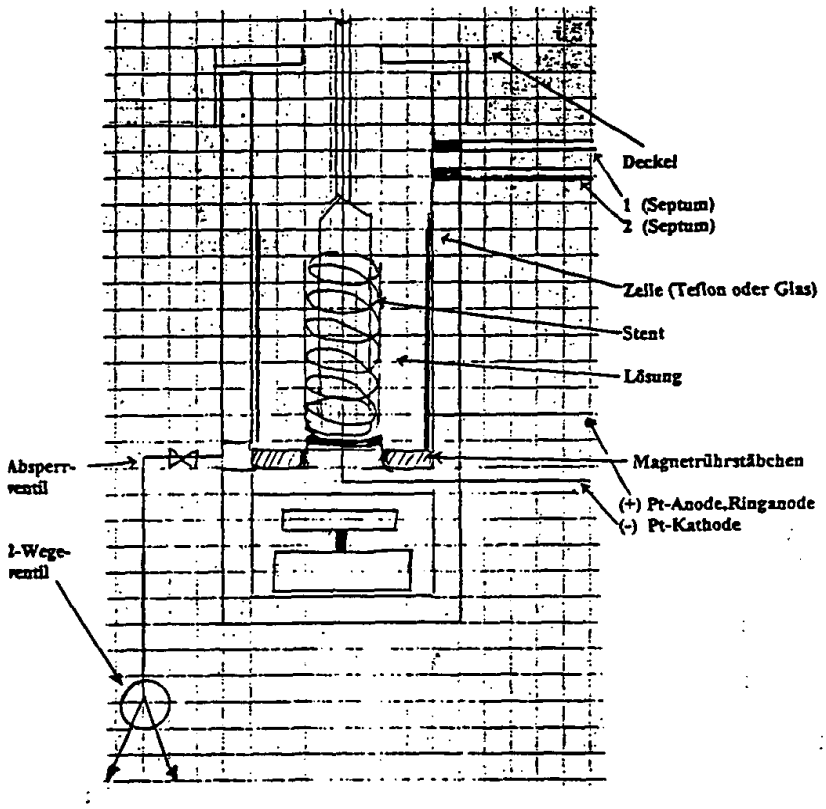
10. Use of radioactive stents that are coated on the surface with radioactive isotopes for the production of an implant for restenosis prophylaxis.

Stents with a Radioactive Surface Coating, Processes for their Production and their Use for Restenosis Prophylaxis

Abstract

The invention relates to radioactive stents, characterized in that the stent is coated on the surface with the radioactive isotope, as well as processes for their production.

Galvanization Cell (Fig. 1)



Addition of solutions: Hypodermic syringes or metering pumps

When addition is done with hypodermic syringes: Put septa in the cover.

If electrolysis is carried out at an elevated temperature, the solution is preheated.

1: Rinsing liquid

2: Active solution

[Key:]

Deckel = cover

Septum = septum

Zelle (Teflon oder Glas) = cell (teflon or glass)

Stent = stent

Lösung = solution

Absperrventil = shutoff valve

2-Wege-ventil = 2-way valve

Magnetrührstäbchen = magnetic stirring rod

(+) Pt-anode, Ringanode = (+) Pt-anode, ring anode

(-) Pt-Kathode = (-) Pt-cathode

Cem ntation Cell (Figs. 2a,b)

Fig. 2a

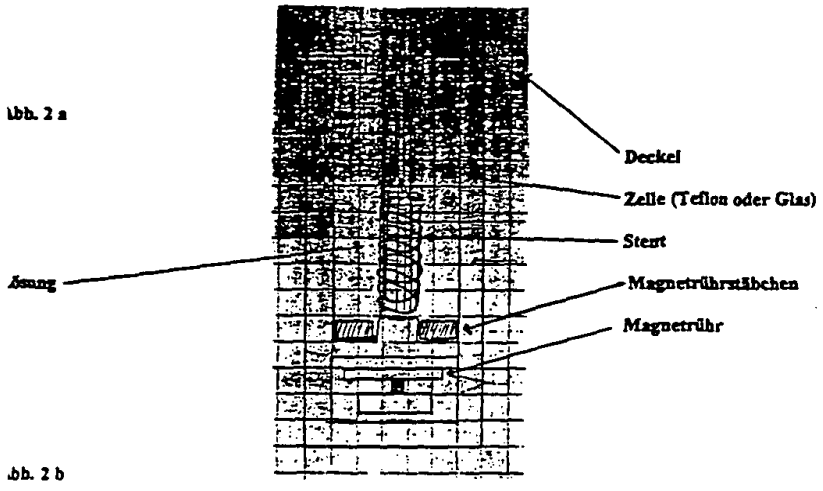
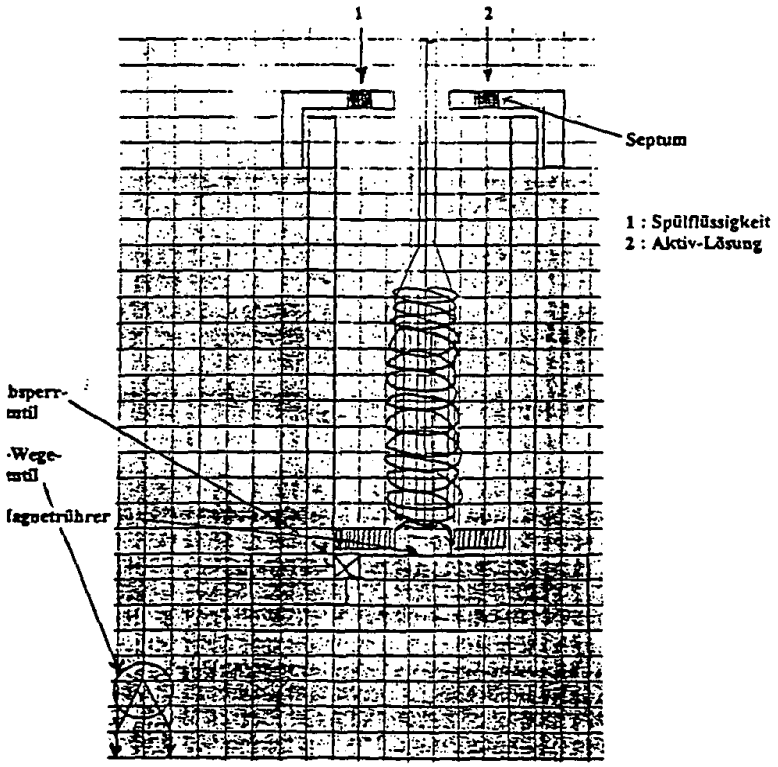


Fig. 2b



[Key to Fig. 2a:]

Deckel = cover

Zelle (Teflon oder Glas) = cell (teflon or glass)

Stent = stent

Magnetrührstäbchen = magnetic stirring rod

Magnetrühr = magnetic stirrer

Lösung = solution

[Key to Fig. 2b:]

Septum = septum

1. Spülflüssigkeit = rinsing liquid

2. Aktiv-Lösung = active solution

Absperrventil = shutoff valve

2-Wege-ventil = 2-way valve

Magnetrührer = magnetic stirrer